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A Phase I Study of Human Lymphoblastoid Interferon in Patients with Hematological Malignancies

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A. Introduction

Objective responses to leukocyte Interferon have now been demonstrated in acute lymphoblastic leukaemia (Hill et al. 1980), chronic lymphocytic leukaemia (Gutterman et al. 1979), myeloma (Mellsted et al. 1979; Idestrom et al. 1979; Osserman and Sherman 1980) and non-Hodgkin's lymphoma (NHL) (Gutterman et al. 1979; Merigan et al. 1978). In 1977 Balkwill and Oliver demonstrated an in vitro cytostatic effect on myeloblasts using human lymphoblastoid interferon (HLBI) (Balkwill and Oliver 1977). This prompted us to undertake a Phase I study of HLBI in patients with acute myeloblastic leukaemia (AML), which is currently in progress. The preliminary results form the basis of this report.

B. Aims

The aims of the study are the following:
1. To determine the maximum tolerated dose of HLBI when given by continuous intravenous infusion;
2. To establish the toxic effects of HLBI given by infusion;
3. To study the pharmacokinetics of HLBI given by intravenous infusion; and
4. To compare the in vitro and in vivo effects of known levels of HLBI in patients with AML.

C. Patients and Methods

Details of the patients studied and the doses administered are shown in Tables 1 and 2.

Table 1. Phase I study of HLBI. Clinical details of 13 patients

Diagnosis	No. of patients
AML	10
NHL – Follicular	1
Myeloma	1
CLL	1
Total	13

Table 2. Phase I study of HLBI. Dosage and scheduling

Patient	HLBI dose (Megaunits/m^2)	No. of days
1	5	Intravenous bolus × 1
2	5	Intravenous bolus × 2
3	3.7	Infusion × 5
4–7	5	Infusion × 5
8–10	7.5	Infusion × 5
11–13	10	Infusion × 5

D. Results

I. Clinical Toxicity

All patients complained of general malaise and anorexia, and all became pyrexial between 2 and 24 h after administration of HLBI. Four patients complained of rigors, 3 of headaches and 1 of joint pains. Patient 2 experienced a hypotensive episode after the second injection of HLBI.

II. Haematological and Biochemical Toxicity

All patients had bone marrow infiltration rendering interpretation of the blood count extremely difficult. In patients with AML, there was a fall in haemoglobin and platelet counts compatible with advancing disease. There was no evidence of renal impairment and liver function tests remained normal throughout.

D. Pharmacokinetic Study

I. Interferon Assay

Interferon activity in serum was measured by reduction of RNA synthesis in V3 cells challenged with Semliki forest virus. Background levels of 10 units/ml were found in pre-treatment sera. Serum interferon levels attained by intravenous injection and infusion are shown in Figures 1, 2 and 3.

E. In Vitro Study

In patients with AML, bone marrow blasts and, where possible, peripheral blood myeloblasts were cultured using a microculture technique with HLBI at concentrations of 10, 10^2, 10^3 and 10^4 units/ml. Growth was assessed by uptake of tritiated thymidine and viable cell counts after 3 days of culture. The degree of growth inhibition with various concentrations of HLBI is shown in Table 3.

Interferon decreased cell survival and inhibited uptake of tritiated thymidine at concentrations greater than 10 units/ml. Growth inhibition was dose dependant. There was no difference in sensitivity between bone marrow and peripheral blood blasts.

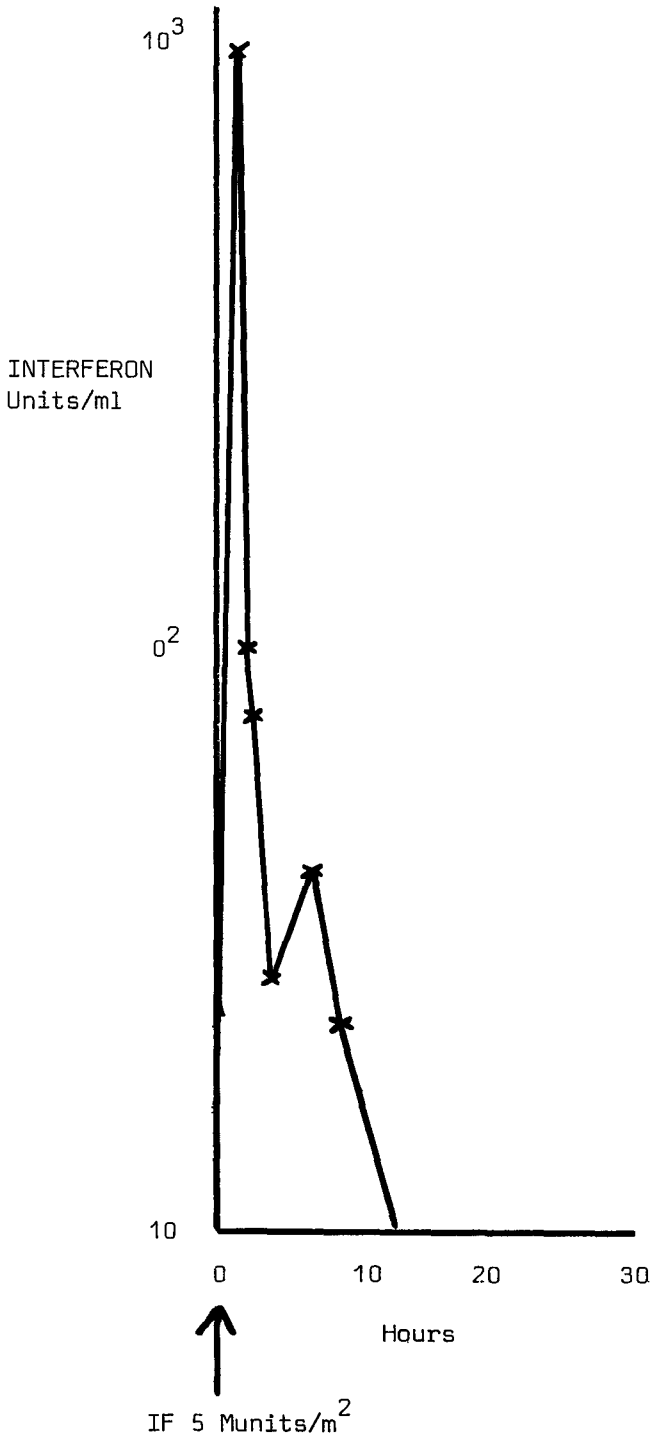

Fig. 1. Interferon levels after injection of 5 Mega-units/m^2 intravenously

F. Conclusions

The symptoms observed are similar to those reported with leukocyte interferon when given intramuscularly. Up to 10×10^6 units/m^2 daily can be given intravenously, but to avoid toxicity and in order to achieve consistent levels intravenous HLBI should be given by continuous infusion.

After intravenous injection of HLBI, high peak levels are achieved at 30 min, but interferon is rapidly cleared in the first h after injection. When given by continuous intravenous infusion, interferon levels increase over 72 h and then remain elevated. Continuous infusion is therefore an appropriate mode of administration for thrombocytopenic patients.

The results of the in vitro study confirm the cell growth inhibitory affects of HLBI on human myeloblasts. The degree of growth inhibition is dose dependant. However, the

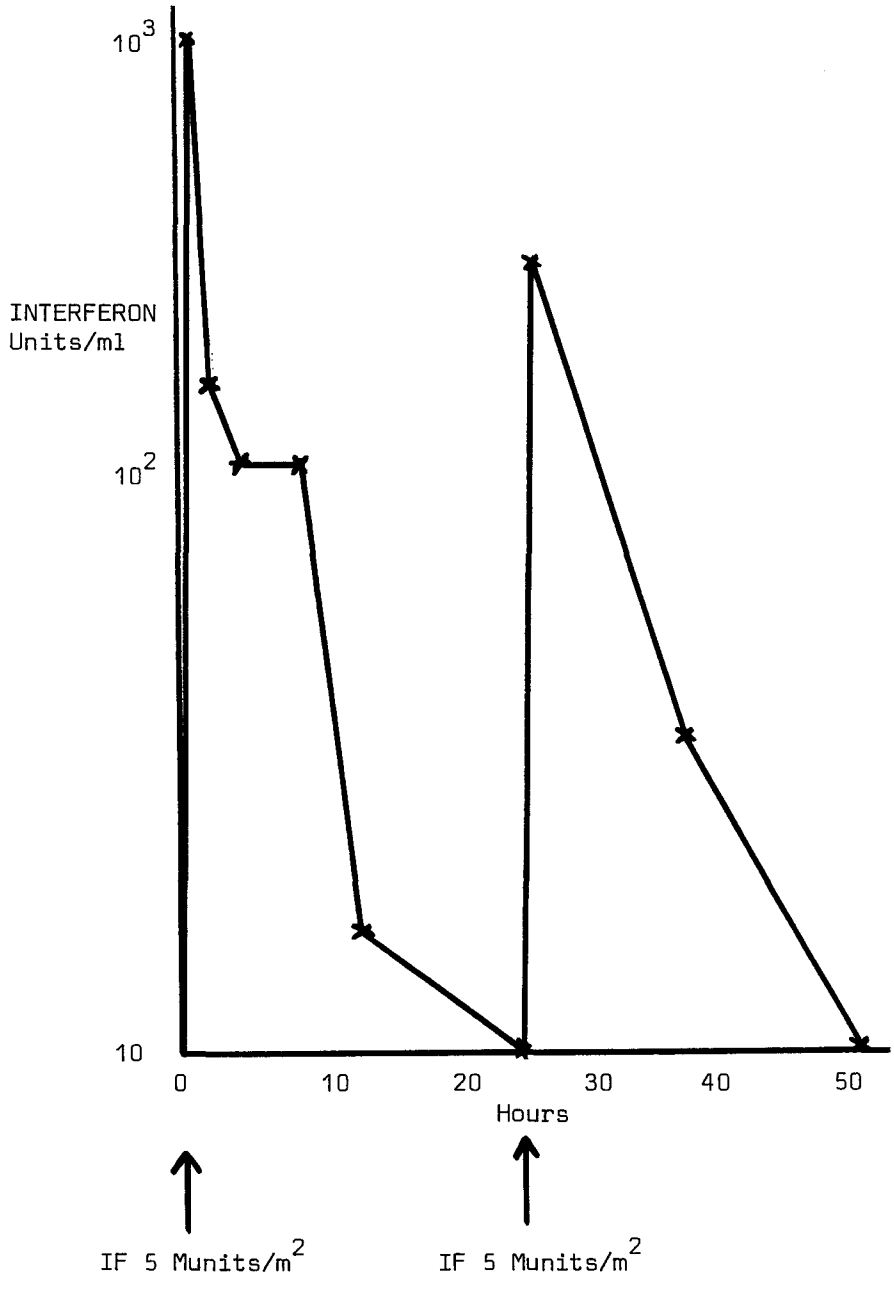

Fig. 2. Interferon levels after injection 5 Megaunits/m^2 intravenously

concentrations of interferon that resulted in 50% inhibiton of growth in vitro were 3–10 times higher than the serum levels attained. With possible further escalation of the dose, levels of 10^3 units/ml may be attainable.

The study continues – it is planned to further escalate the daily dose and duration of infusions up to a maximum of 30 days. Administration of HLBI by subcutaneous injection will also be investigated.

Table 3. The effect of interferon on cell growth and thymidine uptake in bone marrow and peripheral blood myeloblasts

Interferon concentrations (units/ml)				
	10	10^2	10^3	10^4
% Reduction of control cell numbers				
Median	5.7	19.1	41.5	61.6
Range	0–18.3	2.5–38.0	8.4–60.3	28.2–84
% Reduction of thymidine incorporation				
Median	10.4	22.8	39.8	51.3
Range	0–33.2	2.4–38.1	12.9–59.1	28.8–69

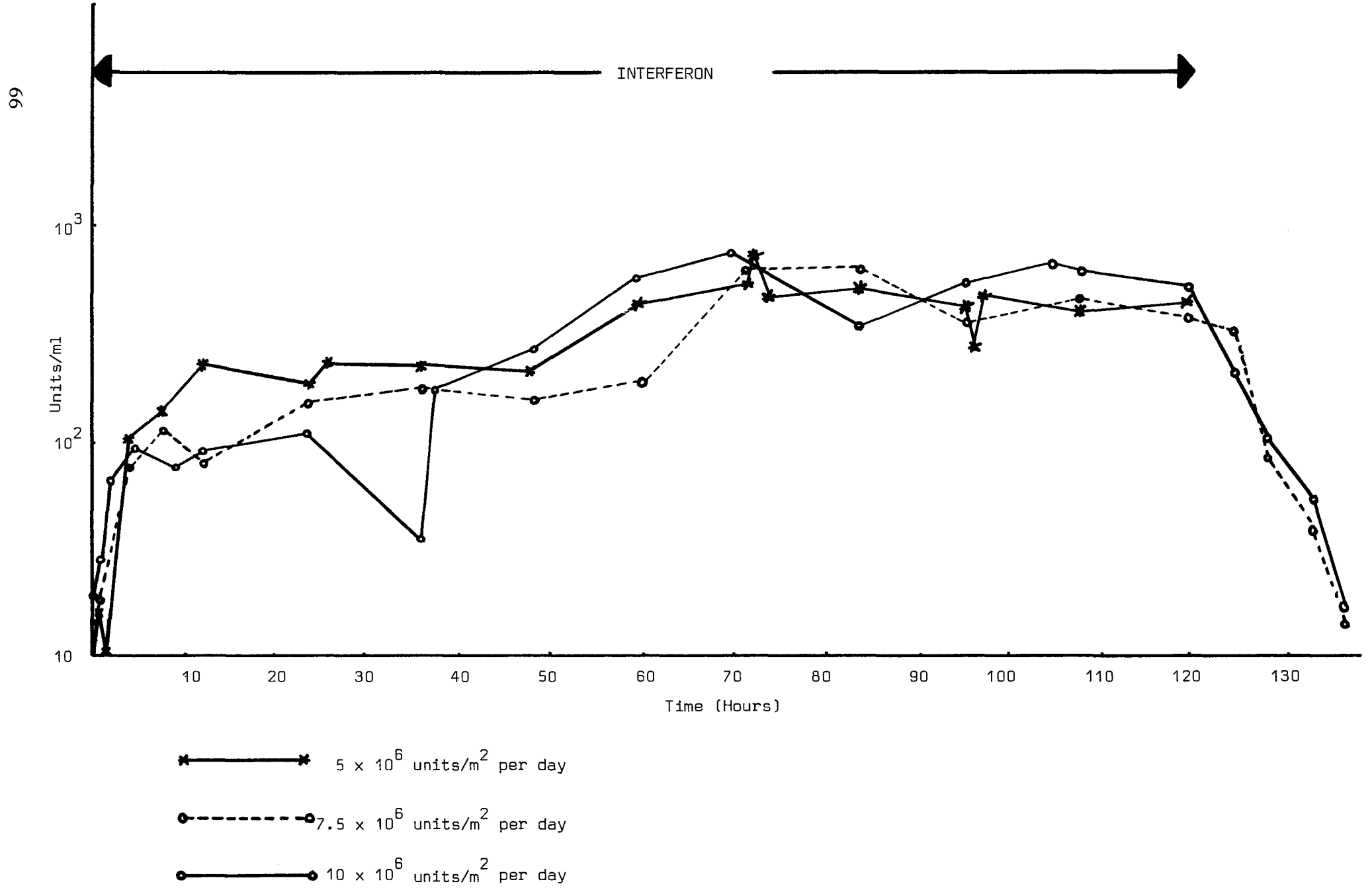

Fig. 3. Interferon levels with continuous infusions of HLBI at different doses

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